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(19)

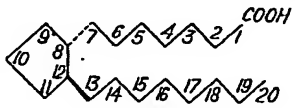
(54) CLATHRATE PROSTAGLANDINS AND COMPOSITIONS CONTAINING SAME

(71) We, ONO PHARMACEUTICAL CO., LTD., a corporation of Japan, of 14, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

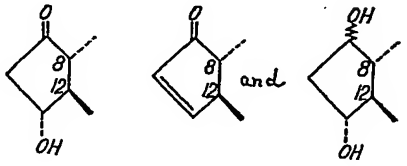
This invention relates to cyclodextrin clathrate compounds of prostaglandins or derivatives thereof, to a process for producing such clathrates and to pharmaceutical compositions containing them.

The prostaglandin group of compounds exists in various tissues of animals. The compounds are newly discovered hormones secreted by the living body itself, and small concentrations of them affect blood pressure, smooth muscle contraction, lipid metabolism, platelet aggregation and gastric secretion.

"Prostaglandin" is a general term for a group of compounds which contain the carbon skeleton of prostanoic acid. The structural formula of prostanoic acid is as follows:



Primary prostaglandins include prostaglandin E_1 (hereinafter referred to as PGE_1), prostaglandin E_2 (hereinafter referred to as PGE_2), prostaglandin A_1 (hereinafter referred to as PGA_1), prostaglandin A_2 (hereinafter referred to as PGA_2), prostaglandin $F_{1\alpha}$ (hereinafter referred to as $PGF_{1\alpha}$), and prostaglandin $F_{2\alpha}$ (hereinafter referred to as $PGF_{2\alpha}$), which naturally occur in the living body and have strong pharmacological activities. The alicyclic five-membered rings of PGE, PGA and PGF compounds have the structures:



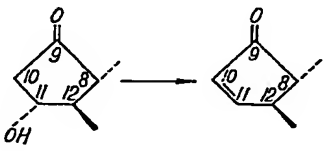
respectively.

These compounds are useful as hypotensive agents, remedies for gastric ulcer, contraceptives, labour-inducing agents, anti-thrombotic agents and remedies for asthma. Thus, more particularly, PGE_1 and PGE_2 are useful as hypotensive agents, remedies for gastric ulcer, remedies for asthma, contraceptives and labour-inducing agents. PGE_1 is also useful as an anti-thrombotic agent, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ as contraceptives and labour-inducing agents, and PGA_1 and PGA_2 as hypotensive agents.

Furthermore, compounds containing carbon skeletons similar to that of prastanoic acid have biological activities similar to that of the prostaglandins, and some of them are more active than the primary prostaglandins. For example, the compounds in which a methyl group is introduced on the carbon atom in the 15- or 16-position of the prostanoic carbon skeleton usually have stronger activity and greater longevity of effect than the corresponding prostaglandin. ω-Homo PGE_1 is better at inhibiting platelet aggregation than PGE_1. When the functional groups of prostaglandins or compounds containing carbon skeletons similar to that of prostanoic acid are substituted by other functional groups, the resulting compounds may also exhibit excellent activity. For example, the decyl esters of PGE_1 and PGE_2, which are described and claimed in the Specification of our Application No. 26850/71 (Serial No. 1,348,162), exhibit a lasting gastric secretion inhibiting effect, and

when used in therapy for the treatment of gastric ulcer, their side effects, i.e., hypotensive effect and smooth muscle contraction effect, are far less marked than those of PGE_2. Furthermore, PGE_2 9-ethoxycarbonylnonyl ester exhibits a greater effect than PGE_2 in asthma therapy. Moreover, conversion of PGA_2 into its decyl ester substantially prolongs the duration of the diuretic and hypotensive effects of the primary prostaglandin as is disclosed in our Application No. 26851/71 (Serial No. 1,348,163).

As described above, prostaglandins and derivatives thereof have many remedial uses. However, they are unstable and, therefore, there is difficulty in compounding them into pharmaceutical forms. Among the naturally occurring prostaglandins, the PGE group is most unstable because the OH group present on the five-membered ring is easily eliminated under the influence of the C—9 carbonyl group as shown by the following formulae:



The elimination of the OH group results in the formation of prostaglandin A containing a double bond in the ring. Furthermore, PGE derivatives undergo a similar dehydration effect.

The other prostaglandins and derivatives thereof are also unstable compared with other drugs because of the presence of double bonds or OH groups in their structures. Patents which describe and claim prostaglandins and derivatives thereof are, for example, British Patents Nos. 851,827, 1,040,544, 1,097,157, 1,097,533 and 1,172,200.

By reacting prostaglandins and analogues thereof with various host molecules, we examined whether clathrates were formed or not and investigated the structures and stabilities of any resulting clathrates. As a result, we have found that cyclodextrin clathrates of prostaglandins or derivatives thereof are obtained as white powdery substances and that each of the resulting clathrate compounds is highly stable.

The above finding is unexpected because when urea or thiourea is used for the host, prostaglandins or derivatives thereof do not form clathrate compounds therewith. Clathrate compounds of urea or cyclodextrin have been used to stabilize various other substances. The formation of such clathrates are considered to be effective in preventing photo-oxidative decomposition of a double bond or the like, but the fact that cyclodextrin clathrate compounds effectively prevent the elimination of OH group as in this invention has never been known.

In accordance with this invention there is provided a cyclodextrin clathrate of a prostaglandin or a derivative of a prostaglandin. The percentage of prostaglandin in the clathrate can vary considerably, but is suitably from 2% to 12% by weight.

The present invention also provides a process for producing such clathrates which comprises reacting cyclodextrin with a prostaglandin or a derivative of a prostaglandin.

The prostaglandin (hereinafter by "prostaglandin" we also mean derivatives of prostaglandin) in producing clathrates according to this invention are those which contain the carbon skeleton of prostanoic acid or ones similar to that of prostanoic acid. Preferably the prostaglandin is one in which the side chain attached to the alicyclic ring has a double bond (preferably trans) between the carbon atoms in the 13 and 14-positions and a hydroxy radical on the carbon atom in the 15-position. The prostaglandins may have a methyl group introduced in the side chain, for example, in the α-position in relation to the carboxy group, or on the carbon atom in the 15, 16 or 17-position. Furthermore, the carboxylic acid group present in the prostaglandins may be esterified with bulky substituent groups, for example the decyl or 9-ethoxycarbonylnonyl group, preferably the former, or the carboxylic acid group may be replaced by a hydroxymethylene group, i.e. $-CH_2OH$ (commonly known as "prostaglandin alcohols").

With regard to the cyclodextrin to be used, any of α, β- or γ-cyclodextrin, or a mixture of any two or three of them, may be used for producing the clathrate compounds. Preferably β-cyclodextrin is employed.

In preparing the clathrate compounds, cyclodextrin is dissolved in water and/or in an organic solvent which is miscible with water and the solution added to a prostaglandin dissolved in an organic solvent which is miscible with water, e.g. ethanol. After the mixture is heated, the clathrate product may be obtained by concentrating the mixture under reduced pressure or leaving it to cool. Preferably 4 to 12 moles of cyclodextrin are used for each mole of prostaglandin. The mixing ratio of organic solvent with water may be suitably varied according to the solubilities of the starting materials and clathrate products. Due to the low thermostabilities of the prostaglandin molecules, it is preferable to conduct the reaction at a temperature below 70° C. In the case of PGE or its derivatives, the preferred reaction temperature is 20—60° C.

The present invention further provides pharmaceutical compositions containing, as the active ingredient, a clathrate of this inven-

tion in association with a pharmaceutical carrier.

The invention will be illustrated by the following examples.

EXAMPLE 1.

350 mg. of β-cyclodextrin were dissolved in 4.7 ml. of water and the solution added to 21.4 mg. of PGE_2 dissolved in 0.3 ml. of ethanol. After the mixture was heated to dissolution at 60° C., it was cooled slowly to room temperature to obtain a precipitate. After standing overnight at room temperature, the precipitate was recovered by filtration and washed with 50% aqueous ethanol and dried under reduced pressure to obtain 300 mg. of desired clathrate product. The content of PGE_2 in the product was 4.7%.

EXAMPLE 2.

A solution prepared by heating and dissolving 523 mg. of β-cyclodextrin in 4.7 ml. of water was added to a solution prepared by dissolving 20.9 mg. of PGE_2 decyl ester in 2.8 ml. of ethanol. The mixture was heated to dissolution at 60° C. and then treated in the same manner as described in Example 1 to obtain the clathrate product. The yield was 180 mg. The content of PGE_2 decyl ester in the product was 9.4%.

EXAMPLE 3.

A solution prepared by heating and dissolving 480 mg. of β-cyclodextrin in 4.7 ml. of water was added to a solution prepared by dissolving 21.7 mg. of PGE_1 decyl ester in 2.8 ml. of ethanol. The mixture was heated to dissolution at 60° C. and then treated in the same manner as described in Example 1 to obtain the clathrate product. The yield was 210 mg. The content of PGE_1 decyl ester was 7.9%.

EXAMPLE 4.

A solution prepared by heating and dissolving 358 mg. of β-cyclodextrin in 4 ml. of water was added to a solution prepared by dissolving 23.8 mg. of PGA_2 in 1.0 ml. of ethanol. The mixture was heated to dissolution at 60° C. and then treated in the same manner as described in Example 1 to obtain the clathrate product. The yield was 230 mg. The content of PGA_2 in the product was 8%.

EXAMPLE 5.

A solution prepared by heating and dissolving 776 mg. of β-cyclodextrin in 6.6 ml. of water was added to a solution prepared by dissolving 28.8 mg. of PGA_2 decyl ester in 4.4 ml. of ethanol. The mixture was heated to dissolution at 60° C., and then treated in the same manner as described in Example 1 to obtain the clathrate product. The yield was 260 mg. The content of PGA_2 decyl ester in the product was 10.8%.

EXAMPLE 6.

A solution prepared by heating and dissolving 340 mg. of β-cyclodextrin in 4.7 ml. of water was added to a solution prepared by dissolving 27 mg. of $PGF_{2\alpha}$ in 0.3 ml. of ethanol. The mixture was heated to dissolution at 60° C., and then treated in the same manner as described in Example 1 to obtain the clathrate product. The yield was 280 mg. The content of $PGF_{2\alpha}$ in the product was 2.6%.

EXAMPLE 7.

A solution prepared by heating and dissolving 526 mg. of β-cyclodextrin in 11.8 ml. of water was added to a solution prepared by dissolving 30.73 mg. of PGE_1 alcohol in 0.3 ml. of ethanol. The mixture was heated to dissolution at 45° C. and then gradually cooled to the room temperature to form a precipitate. After standing overnight at 0° C., the precipitate was recovered by filtration and washed with a 50% aqueous solution of ethanol and dried under reduced pressure to obtain 229 mg. of clathrate product. The content of PGE_1 alcohol in the product was 6.2%.

EXAMPLE 8.

A solution prepared by heating and dissolving 257 mg. of β-cyclodextrin in 6.0 ml. of water was added to a solution prepared by dissolving 16.94 mg. of α-methyl-PGE_1 in 0.2 ml. of ethanol. The mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 103 mg. of clathrate product. The content of α-methyl-PGE_1 in the product was 10.3%.

EXAMPLE 9.

A solution prepared by heating and dissolving 268 mg. of β-cyclodextrin in 6.1 ml. of water was added to a solution prepared by dissolving 25.40 mg. of PGE_2 9-ethoxycarbonylnonyl ester in 0.3 ml. of ethanol. The mixture was heated to dissolution at 45° C. and then treated in the same manner as described in Example 7 to obtain 154 mg. of the clathrate product. The content of PGE_2 9-ethoxycarbonylnonyl ester in the product was 5.9%.

EXAMPLE 10.

A solution prepared by heating and dissolving 251 mg. of β-cyclodextrin in 6.0 ml. of water was added to a solution prepared by dissolving 14.42 mg. of 9 - oxo - 15α-hydroxy - prosta - 5 *cis*, 11,13 - *trans*-trienoic acid (known as PG 234) in 0.2 ml. of ethanol. The mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 143 mg. of clathrate product. The content of PG 234 in the product was 5.5%.

EXAMPLE 11.

A solution prepared by heating and dissolving 255 mg. of β-cyclodextrin in 6.0 ml. of water was added to a solution prepared by dissolving 17.37 mg. of α-methyl-PGE_2 in 0.2 ml. of ethanol and the mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 154 mg. of the clathrate product. The content of α-methyl-PGE_2 in the product was 9.5%.

EXAMPLE 12.

A solution prepared by heating and dissolving 165 mg. of β-cyclodextrin in 3.7 ml. of water was added to a solution prepared by dissolving 10.44 mg. of 16-methyl-PGE_2(B) in 0.2 ml. of ethanol. The mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 159 mg. of the clathrate product. The content of 16-methyl-PGE_2(B) in the product was 12.1%.

The presence of "(B)" after 16-methyl-PGE_2 as indicated above and in Examples 15 and 16 hereafter is explained as follows:

When 16-methyl-PGE_2 is prepared, a mixture of four stereoisomers is obtained due to the configuration of the hydroxy and methyl groups on the C—15 and C—16 carbon atoms respectively. The product when subjected to chromatography on a silica gel column can be divided into two portions, one portion having a higher polarity than the other. The portion having the higher polarity is termed "16-methyl-PGE_2(B)", its stereoconfiguration being unknown.

A similar explanation for the suffix "(B)" after 17-methyl-PGE_2 in Example 13 applies.

EXAMPLE 13.

A solution prepared by heating and dissolving 480 mg. of β-cyclodextrin in 11.0 ml. of water was added to a solution prepared by dissolving 30.21 mg. of 17-methyl-PGE_2(B) in 0.3 ml. of ethanol. The mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 146 mg. of the clathrate product. The content of 17-methyl-PGE_2(B) in the product was 10.8%.

EXAMPLE 14.

A solution prepared by heating and dissolving 490 mg. of β-cyclodextrin in 11.0 ml. of water was added to a solution prepared by dissolving 31.18 mg. of 15-methyl-PGE_2 in 0.3 ml. of ethanol. The mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 285 mg. of the clathrate product. The content of 15-methyl-PGE_2 in the product was 2.3%.

EXAMPLE 15.

A solution prepared by heating and dissolving 224 mg. of β-cyclodextrin in 6.0 ml. of water was added to a solution prepared by dissolving 6.84 mg. of 16-methyl-PGE_2(B) alcohol in 0.2 ml. of ethanol. The mixture was heated to dissolution at 45° C., and was then treated in the same manner as described in Example 7 to obtain 224 mg. of the clathrate product. The content of 16-methyl-PGE_2(B) alcohol in the product was 3.0%.

EXAMPLE 16.

A solution prepared by heating and dissolving 239 mg. of β-cyclodextrin in 6.0 ml. of water was added to a solution prepared by dissolving 6.95 mg. of 16-methyl-PGE_2(B) decyl ester in 0.2 ml. of ethanol. The mixture was heated to dissolution at 45° C., and then treated in the same manner as described in Example 7 to obtain 198 mg. of the clathrate product. The content of 16-methyl-PGE_2-(B) decyl ester in the product was 3.0%.

EXAMPLE 17.

A solution prepared by heating and dissolving 510 mg. of α-cyclodextrin in 2 ml. of water was added to 25.2 mg. of PGE_2 dissolved in 0.3 ml. of ethanol. The mixture was heated to dissolution at 60° C. and then cooled gradually to room temperature to form a precipitate. After standing overnight at 0° C., the precipitate was recovered by filtration, washed with 50% aqueous ethanol and dried under reduced pressure to obtain 261 mg. of the clathrate product. The content of PGE_2 in the product was 6.0%.

EXAMPLE 18.

A solution prepared by heating and dissolving 418 mg. of α-cyclodextrin in 2 ml. of water was added to 20.1 mg. of PGE_1 alcohol dissolved in 0.2 ml. of ethanol. The mixture was heated to dissolution at 60° C. and then cooled gradually to room temperature to form a precipitate. After standing overnight at 0° C., the precipitate was recovered by filtration, washed with 50% aqueous ethanol and dried under reduced pressure to obtain 152 mg. of clathrate product. The content of PGE_1 alcohol in the product was 4.1%.

In all of the above Examples, the clathrate compounds obtained were white powdery substances and their infrared spectra showed absorptions of carbonyl groups at 1710—1740 cm^{-1} in the case of PGE, PGA and their

derivatives. The binding r[redacted] of prostaglandins with cyclodextrin [redacted] clathrates (i.e. content of prostaglandins in the products) were determined by quantitative analysis of the prostaglandins in the clathrate compounds. The quantitative analysis was conducted in the following manner. PGA, PGE and their derivatives were isomerized with alkali to PGB and the resulting absorption values in UV spectra were determined at wavelength 278 mμ. In the case of PGF, a contraction of guinea pig colon was employed in the determination.

It was confirmed by heat stabi[redacted]tests that the clathrates of this invention h[redacted]good stabilities compared with the original prostaglandis. Table 1 shows the contents of various PGs in the clathrate compounds and results of stability tests when heated at 106±4° C. when cyclodextrin is used as a host molecule.

Heat stability tests of various cyclodextrin clathrates of this invention gave good results regardless of the type of cyclodextrin used.

TABLE 1

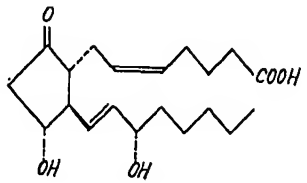
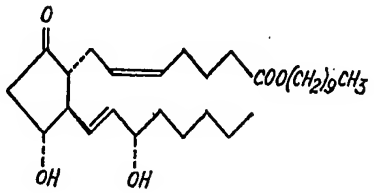
Prostaglandin	Content*1		Heat Stability *2			
			1 hour	3 hours	8 hours	30 hours
PGE_2 	4.7%	PG—CD*3	97.5%	92.8%	90.6%	
		PG*4	77.0	55.0	29.8	
PGE_2 decyl ester 	9.4	PG—CD	98.1	96.8	95.2	
		PG	94.5	89.1	72.3	

TABLE 1 (continued)

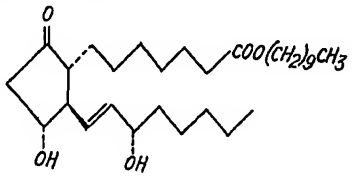
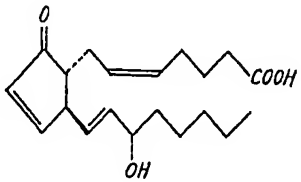
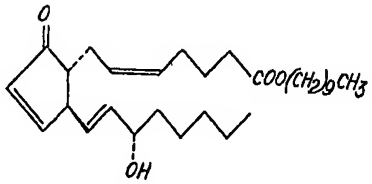
Prostaglandin	Content*1		Heat Stability *2 1 hour	3 hours	8 hours	30 hours
PGE_1 decyl ester 	7.9	PG—CD	99.2	98.5	97.2	
		PG	95.2	89.9	73.4	
PGA_2 	8.0	PG—CD	99.8	98.8	98.1	
		PG	99.4	98.3	95.6	
PGA_2 decyl ester 	10.8	PG—CD	99.8	99.2	98.6	
		PG	99.5	98.6	97.0	

TABLE 1 (continued)

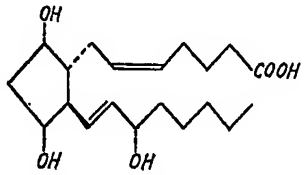
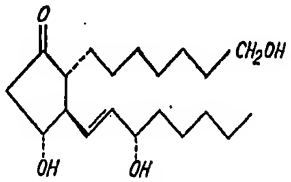
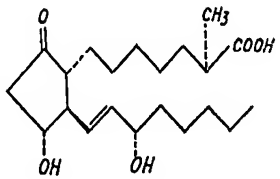
Prostaglandin	Content *1		Heat Stability *2 1 hour	3 hours	8 hours	30 hours
PGF_α 	2.6	PG—CD	100	100	99	
		PG	100	99	99	
PGE_1 alcohol 	6 2	PG—CD*3	92.9	92.8	88.0	79.1%
		PG*4	95.4	93.8	84.9	59.8
α-methyl-PGE_1 	10.3	PG—CD	97.4	88.5	90.5	
		PG	82.1	69.2	55.2	

TABLE 1 (continued)

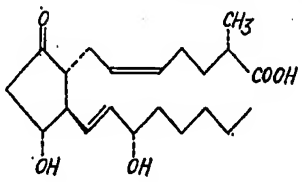
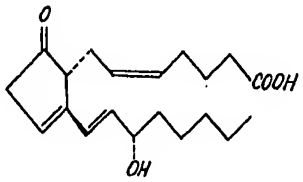
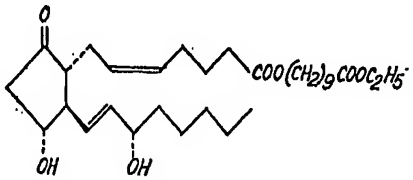
Prostaglandin	Content *1		Heat Stability *2 1 hour	3 hours	8 hours	30 hours
α-methyl-PGE_2 	9.5	PG—CD	96.6	92.5	91.9	
		PG	94.4	69.1	61.7	
PG 234 	5.6	PG—CD	96.3	96.3	95.6	
		PG	54.9	48.8	46.0	
PGE_2 9-ethoxycarbonylnonyl ester 	5.9	PG—CD	100.0	96.4	97.3	94.2
		PG	97.5	93.8	90.8	69.6

TABLE 1 (continued)

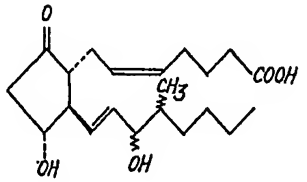
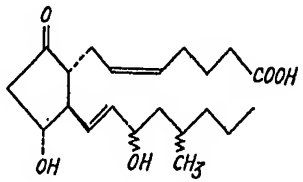
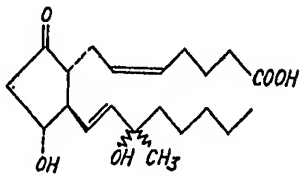
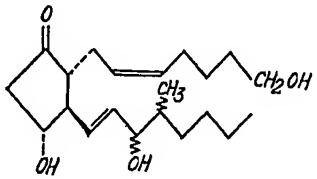
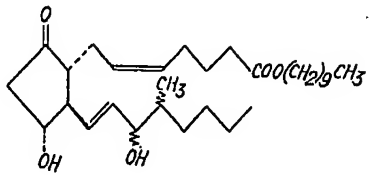
Prostaglandin	Content *1		Heat Stability *2 1 hour	3 hours	8 hours	30 hours
16-methyl-PGE_2 (β) 	12.1	PG—CD	97.8	92.1	87.9	
		PG	75.9	62.9	45.6	
17-methyl-PGE_2 (β) 	10.8	PG—CD	98.7	97.9	97.4	
		PG	76.9	66.7	59.9	
15-methyl-PGE_2 	2.3	PG—CD	86.8	86.5	83.4	
		PG	65.4	49.4	43.6	

TABLE 1 (continued)

Prostaglandin	Content *1		Heat Stability *2 1 hour	3 hours	8 hours	30 hours
16-methyl-PGE_2 (β) alcohol 	3.0	PG—CD	98.7	90.9	91.9	
		PG	84.4	66.2	63.0	
16-methyl-PGE_2 (β) decyl ester 	3.0					

*1: The prostaglandin is represented by the percentage (w/w) of prostaglandins in the clathrate compounds.
*2: The percentage of prostaglandin remaining stable at 106°±4°C.
*3: PG—CD represents cyclodextrin clathrate compounds of the prostaglandins.
*4: PG represents the prostaglandins.

As shown in Table 1, there is a great variety in content of prostaglandin in the clathrate compounds according to structures of the compounds. With regard to the heat stabilities, the clathrate compounds are shown to be much more stable than the original prostaglandins. Such stable prostaglandins have never been known. It is significant in this respect that(according to the invention, the use of cyclodextrin clathrates is the first way in which prostaglandins have been embodied in pharmaceutical forms. Since all the clathrate compounds obtained are white powdery substances and are easy to handle they may be employed in various pharmaceutical formulations, e.g. injectable compositions, tablets, aerosols, powders, capsules or suspensions.

The following Examples illustrate some procedures for making the clathrate compounds of this invention into pharmaceutical formulations.

EXAMPLE 19.

PGE_2-cyclodextrin (Vaginal Suppository)

Avicel — a registered Trade Mark (micro-crystalline cellulose)	10 g.
Mannite	12.5 g.
Tartaric acid	10 g.
Sodium Bicarbonate	10 g.
ECG (Calcium carboxylmethylcellulose)	2 g.

Granules were made by well mixing the above ingredients and adding to the mixture 0.5 g. of PVP (polyvinylpyrrolidone) dissolved in a small amount of methanol as a binder. After satisfactorily drying, the granules were passed through a 12-mesh sieve to obtain uniform size granules. To these granules were added the following ingredients:

PGE_2—CD (PG content 8%)	2.5 g.
ECG 505 (Calcium carboxymethylcellulose)	2 g.
Magnesium stearate	0.5 g.

Effervescent vaginal suppositories containing 2 mg. of PGE_2 in each tablet were obtained by tableting 500 mg. samples of the mixture.

EXAMPLE 20.

PGE_2-cyclodextrin tablet

Granules were made by well mixing 17.5 g. of lactose and 3.89 g. of starch and adding HPC (hydroxypropylcellulose) in 0.5 g. of methanol as a binder. After satisfactorily drying, the granules were sieved through a 12-mesh sieve to obtain uniform size granules. After adding to the granules 2.86 g. of PGE_2-cyclodextrin (PG content 7%) and 250 mg. of magnesium stearate, tablets were made, each being 8.5 mm. in diameter and 250 mg. in weight. Each tablet contained 2 mg. of PGE_2.

EXAMPLE 21.

PGE_2 decyl ester-cyclodextrin capsule

PGE_2 decyl ester-cyclodextrin (PG content 9.4%)	0.43 g.
Mannite	3 g.
Corn starch	0.4 g.

The above substances were well mixed and sieved through a 32-mesh sieve several times. After that, 220 mg. batches of the mixture were packed into No. 3 hard capsules. Each capsule contained 2 mg. of PGE_2 decyl ester.

EXAMPLE 22.

PGE_2-cyclodextrin Injectable Composition

Powdery PGE_2-cyclodextrin (PG content 8%) was subdivided, under sterile conditions, into ampoules so that each ampoule contained 12.5 mg. The air inside each ampoule was substituted by nitrogen gas and the ampoule sealed. The content of the ampoule was useful as an injectable composition containing 1 mg. of PGE_2 when dissolved in a 0.9% saline solution for injection.

EXAMPLE 23.

$PGF_{2\alpha}$-cyclodextrin Powder

$PGF_{2\alpha}$-cyclodextrin (PG content 2%)	20 g.
Potato Starch	90 g.

The above substances were mixed well and sieved through a 42-mesh sieve. Then 400 g. of lactose were added to the mixture, the whole sieved through the 42-mesh sieve and mixed again to obtain 0.1% $PGF_{2\alpha}$ powder.

It is also possible to make a pharmaceutical preparation comprising a mixture of the clathrates of this invention and free cyclodextrin by using an excess of cyclodextrin in the reaction with prostaglandins or their analogues.

The biological activities of the clathrates of this invention, that is to say, hypotensive effects, contractive effects of uterine or intestinal smooth muscle and gastric secretion inhibiting effects, were very similar to those of the original prostaglandins and the toxicity of the cyclodextrin is so low that if intravenously injected into male mice at dosage of more than 1 g./kg., none of them dies. Consequently, there is no obstacle in the application of these clathrate compounds for medical use.

As explained above the clathrates of this invention are useful as various therapeutic preparations in various pharmaceutical forms. The administrative dosage may vary over a wide range depending upon the particular prostaglandin compound used, particular manner of administration, particular pharmaceutical form and particular condition to be treated. The following examples illustrate some typical actual uses of the agents.

Labour-inducing a[redacted]

A labour-inducing agent [redacted]e form of vaginal suppository, tablet, capsule or powder containing PGE_2-cyclodextrin may be administered in a total amount of 60—120 mg. (as PGE_2-cyclodextrin), divided into 3—6 doses at intervals of about 2—3 hours. A suppository is inserted in the vagina, whilst the tablet, capsule or powder forms may be administered orally. In case of infusion, the administration is conducted for a long time and in an amount of 5—30 mg.

PGF_{2a}-cyclodextrin may be administered in the same manner except that the total dosage in the form of a suppository, tablet, capsule or powder, is from 250 mg.—5 g., whilst in the case of infusion it is from 100 mg.—1 g.

Contraceptive.

A contraceptive agent in the form of vaginal suppository, tablet, capsule or powder, containing PGF_2-cyclodextrin may be administered in a total amount of 200 mg. to 1.2 g. (as PGE_2-cyclodextrin), divided into 2—3 doses at intervals of about 2—3 hours. A suppository is inserted in the vagina, whilst tablets, capsules, or powders are administered orally. In case of infusion, the administration is conducted for a long time with a total dosage of 20 mg.—150 mg.

PGF_{2a}-cyclodextrin may be administered in the same manner except that the total dosage in the form of suppository, tablet, capsule or powder is 1—8 g. while in the case of infusion it is 500 mg.—5 g.

Remedy for Ulcer.

For ulcer relief, PGE_2-cyclodextrin in the form of tablet, capsule or powder may be continuously and orally administered with a dosage of 5—50 mg. (as PGE_2-cyclodextrin)/day/adult.

PGE_2 decyl ester-cyclodextrin may be administered in the same manner except that the dosage is from 40—400 mg./day/adult.

Hypotensive-agent.

As a hypotensive agent, PGE_2-cyclodextrin in the form of tablets, capsules, or powders may be administered orally in an amount of 2.5—25 mg. (as PGE_2-cyclodextrin). In case of intramuscular injection the dosage may be from 1—10 mg.

PGA_2 decyl ester-cyclodextrin may be administered orally in the same manner except that the dosage is from 20—200 mg.

Remedy for asthma.

For the relief of asthma, an aerosol agent containing PGE_1 alcohol-cyclodextrin and/or PGE_2 9-ethoxycarbonylnonyl ester-cyclodextrin may be sprayed in an amount of 100 μg. to 500 μg. (as the clathrate compound) at a time.

WHAT WE CLAIM IS:—

1. A cyclodextrin clathrate of a [redacted]ostaglandin or of a derivative of a prostaglandin.

2. A cyclodextrin clathrate of a prostaglandin or of a derivative of a prostaglandin in which the alicyclic ring of the prostaglandin or the derivative of a prostaglandin is that of a PGE compound.

3. A cyclodextrin clathrate of a prostaglandin or of a derivative of a prostaglandin in which the alicyclic ring of the prostaglandin or the derivative of a prostaglandin is that of a PGF compound.

4. A cyclodextrin clathrate of a prostaglandin or of a derivative of a prostaglandin in which the alicyclic ring of the prostaglandin or the derivative of a prostaglandin is that of a PGA compound.

5. A cyclodextrin clathrate of a prostaglandin or a derivative of a prostaglandin according to any one of claims 1 to 4 in which the side chain attached to the alicyclic ring has a double bond between the carbon atoms in the 13- and 14-positions and a hydroxy radical on the carbon atom in the 15-position.

6. A cyclodextrin clathrate of a prostaglandin derivative according to any one of claims 1 to 5 which carries a methyl substituent on the carbon atom in α-position to the carboxy group, or on the carbon atom in the 15-, 16- or 17-position of the prostaglandin derivative.

7. A cyclodextrin clathrate of a prostaglandin derivative according to any one of claims 1 to 6 in which the carboxy radical is esterified with a decyl group.

8. A cyclodextrin clathrate of a prostaglandin derivative according to any one of claims 1 to 6 in which the carboxy radical of the prostaglandin is replaced by a hydroxymethylene group.

9. A cyclodextrin clathrate of a prostaglandin or of a derivative of a prostaglandin according to any one of claims 1 to 8 in which the clathrate is formed with β-cyclodextrin.

10. The β-cyclodextrin clathrate of PGE_2 or PGE_2 decyl ester.

11. The β-cyclodextrin clathrate of PGE_1 alcohol.

12. The β-cyclodextrin clathrate of PGE_1 decyl ester.

13. The β-cyclodextrin clathrate of PGA_2 or PGA_2 decyl ester.

14. The β-cyclodextrin clathrate of PGF_{2a}.

15. The β-cyclodextrin clathrate of α-methyl-PGE_1.

16. The β-cyclodextrin clathrate of PGE_2 9-ethoxycarbonylnonyl ester.

17. The β-cyclodextrin clathrate of 9-oxo-15α-hydroxy-prosta-5-cis, 11,13-trans-trienoic acid.

18. The β-cyclodextrin clathrate of α-methyl-PGE_2.

19. The [redacted]yclodextrin clathrate of 15-methyl-PGE_2, 16-methyl-PGE_2(B) or 17-methyl-PGE_2(B).

20. The β-cyclodextrin clathrate of 16-methyl-PGE_2(B) alcohol or 16-methyl-PGE_2-(B) decyl ester.

21. The α-cyclodextrin clathrate of PGE_2.

22. The α-cyclodextrin clathrate of PGE_1 alcohol.

23. A cyclodextrin clathrate of a prostaglandin or of a derivative of a prostaglandin according to any one of the preceding claims in which the prostaglandin content of the clathrate is from 2.0% to 12% by weight of the clathrate.

24. A process for the production of a cyclodextrin clathrate as claimed in any one of claims 1 to 23 which comprises reacting a prostaglandin or a derivative thereof with cyclodextrin.

25. A process according to claim 24 in which a solution of the cyclodextrin in water and/or in an organic solvent which is miscible with water is added to a solution of the prostaglandin or derivative thereof in an organic solvent which is miscible with water, the mixture is heated at a temperature below 70° C., and the resulting cyclodextrin clathrate of the prostaglandin or derivative thereof is separated from the reaction mixture.

26. A process according to claim 25 in which the prostaglandin or derivative thereof is a PGE compound and the reaction is carried out at a temperature of 20—60° C.

27. A process [redacted]rding to claim 25 or 26 in which the organic solvent is ethanol.

28. A process according to claim 24, 25, 26 or 27 in which the molar ratio of prostaglandin to cyclodextrin in the reaction mixture is 1:4 to 12.

29. A process according to any one of claims 24 to 28 in which the cyclodextrin is β-cyclodextrin

30. A process for the production of cyclodextrin clathrates of prostaglandins or derivatives thereof according to claim 24 substantially as hereinbefore described in any one of Examples 1 to 18.

31. Cyclodextrin clathrates of prostaglandins or derivatives thereof when produced by the process claimed in any one of claims 24 to 30.

32. A pharmaceutical composition comprising, as active ingredient, a clathrate as claimed in any one of claims 1 to 23 in association with a pharmaceutically acceptable carrier.

33. A pharmaceutical composition according to claim 32 substantially as hereinbefore described with especial reference to any one of Examples 19 to 23.

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